

REMARKS

Claims 1-7, 16-17 and 22-25 are currently pending in the application. Claims 1 and 7 have been amended. Claim 1 has been amended to more particularly point out that a combination of ORP and BNP or N-BNP is used to determine an increased risk of heart disease. Support for the amendment to claim 1 can be found in the original specification and claims, *e.g.*, paragraphs [0103-0110] and Tables II and III. Claims 22-25 have been withdrawn without prejudice. No new matter has been added by these amendments.

Claim Rejections – 35 U.S.C. § 112, first paragraph - enablement

Claims 1-7 and 16-17 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement, because the specification is allegedly not enabling for any “N-BNP” or “BNP” without reference to a specific polypeptide sequence for the recited “N-BNP,” or “BNP.” Applicants have amended claim 1 to recite SEQ ID numbers for BNP and N-BNP, and have amended the sequence listing to include the amino acid sequences for these polypeptides. Accordingly, Applicants request the reconsideration and withdrawal of the rejections for lack of enablement.

Claim Rejections – 35 U.S.C. § 112, first paragraph - written description

Claims 1-8 and 10-17 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, it is alleged that there is no written description for embodiments wherein an antibody is specific for “N-BNP” or “BNP.” As described above, Applicants have amended claim 1 to recite SEQ ID numbers for BNP and N-BNP, and have amended the sequence listing to include the amino acid sequences for these polypeptides. In view of these amendments, Applicants request the reconsideration and withdrawal of the rejections for lack of written description.

Claim Rejections – 35 U.S.C. § 103

Claims 1-4, 7 and 16-17 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,948,637 in view of Hall et al. The Examiner states that it would have been obvious to one of ordinary skill in the art to combine the determination of ORP150 from the teachings of the ‘637 patent with the determination of other diagnostic markers, such as BNP and N-BNP, for diagnosis of heart failure in view of the suggestion in Hall to combine tests to improve diagnostic performance. (Office Action at pages 9-10). The

Examiner also states that from the combined teachings of the '637 patent and Hall, one of skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Claim 1 as currently amended provides a method for detecting tissue hypoxia in a mammalian subject by (a) contacting a bodily fluid sample with an antibody specific for an oxygen related protein 150 (ORP150) comprising SEQ ID NO: 2 in order to detect the level of ORP150 in the bodily fluid sample and (b) contacting a bodily fluid sample with an antibody specific for a brain natriuretic peptide (BNP) comprising SEQ ID NO: 4 or a N-terminal pro-brain natriuretic peptide (N-BNP) comprising SEQ ID NO: 5. The method comprises determining an increased risk of heart disease in the subject if the level of ORP150 is at least 956 fmol/ml and the level of brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (N-BNP) is at least 5.7 fmol/ml.

The '637 patent shows human and rat ORP150 proteins and the amino acid sequences thereof. The '637 patent also shows a polypeptide obtainable by inducement under hypoxic conditions. Hall discusses the potential value of natriuretic peptides for estimation of long-term prognosis, for therapeutic monitoring, and as indication for treatment.

The '637 patent fails to teach or suggest detecting any specific level of ORP150, much less a level of ORP150 of at least 956 fmol/ml in a bodily fluid sample. Similarly, Hall is silent on detecting any specific level of BNP or N-BNP, including a level of at least 5.7 fmol/ml of BNP or N-BNP in the bodily fluid sample. Nor would one of skill in the art have a reasonable expectation of success of combining the teachings of the '637 patent and Hall to arrive at these cut-off levels of detection. Further, the instant specification teaches that the claimed combination of ORP150 and N-BNP surprisingly provides detection of heart failure with higher specificity than either of the peptides alone: at 95% sensitivity, specificity for the combination of ORP150 and N-BNP is 68.3%, while the specificities for N-BNP and ORP150 are only 40.6 and 39.4% respectively. (See instant application at paragraphs [0106-0108].)

For these reasons, Applicants assert that one of skill in the art would not produce the claimed methods by the combination of the '637 patent and Hall. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection for obviousness over U.S. Patent No. 5,948,637 in view of Hall.

Claims 4-5 stand as rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,948,637 in view of Hall and further in view of Karl et al.

As discussed above, the combination of the '637 patent with Hall does not render claims 1-4, 7 and 16-17 obvious. The addition of Karl et al does not remedy this deficiency.

Thus, Applicants respectfully request reconsideration and withdrawal of the rejection for obviousness over U.S. Patent No. 5,948,637 in view of Hall and further in view of Karl et al.

Claims 4 and 6 stand as rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,948,637 in view of Hall and further in view of May et al.

As discussed above, the combination of the '637 patent with Hall does not render claims 1-4, 7 and 16-17 obvious. The addition of May et al does not remedy this deficiency.

Thus, Applicants respectfully request reconsideration and withdrawal of the rejection for obviousness over U.S. Patent No. 5,948,637 in view of Hall and further in view of May et al.

CONCLUSION

Early and favorable consideration of the application is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at (617) 832-1000.

Respectfully submitted,
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